Tobacco, Alcohol, and Socioeconomic Status and Adenocarcinomas of the Esophagus and Gastric Cardia

*Marilie D. Gammon, Janet B. Schoenberg, Habibul Ahsan, Harvey A. Risch, Thomas L. Vaughan, Wong-Ho Chow, Heidi Rotterdam, A. Brian West, Robert Dubrow, Janet L. Stanford, Susan T. Mayne, Diana C. Farrow, Shelley Niwa, William J. Blot, Joseph F. Fraumeni, Jr.**

Background: **Incidence rates for adenocarcinomas of the esophagus and gastric cardia have risen steeply over the last few decades. To determine risk factors for these tumors, we conducted a multicenter, population-based, case–control study.** ***Methods:*** **The study included 554 subjects newly diagnosed with esophageal or gastric cardia adenocarcinomas, 589 subjects newly diagnosed with esophageal squamous cell carcinoma or other gastric adenocarcinomas, and 695 control subjects. Estimates of risk (odds ratios [ORs] and corresponding 95% confidence intervals [CIs]) were calculated for the four tumor types separately and for esophageal and gastric cardia adenocarcinomas combined.** ***Results:*** **Risk of esophageal and gastric cardia adenocarcinomas combined was increased among current cigarette smokers (OR = 2.4; 95% = 1.7–3.4), with little reduction observed until 30 years after smoking cessation; this risk rose with increasing intensity and duration of smoking. Risk of these tumors was not related to beer (OR = 0.8; 95% CI = 0.6–1.1) or liquor (OR = 1.1; 95% CI = 0.8–1.4) consumption, but it was reduced for drinking wine (OR = 0.6; 95% CI = 0.5–0.8). Similar ORs were obtained for the development of noncardia gastric adenocarcinomas in relation to tobacco and alcohol use, but higher ORs were obtained for the development of esophageal squamous cell carcinomas. For all four tumor types, risks were higher among those with low income or education.** ***Conclusions:*** **Smoking is a major risk factor for esophageal and gastric cardia adenocarcinomas, accounting for approximately 40% of cases.** ***Implications:*** **Because of the long lag time before risk of these tumors is reduced among ex-smokers, smoking may affect early stage carcinogenesis. The increase in smoking prevalence during the first two thirds of this century may be reflected in the rising incidence of these tumors in the past few decades among older individuals. The recent decrease in smoking may not yet have had an impact.** **[J Natl Cancer Inst 1997;89:1277–84]**

The incidence rates for adenocarcinomas of the esophagus and gastric cardia have risen steeply in the United States and Europe during the past few decades, whereas the incidence of squamous cell carcinoma of the esophagus and of adenocarcinomas located elsewhere in the stomach have remained stable or have decreased during this time period *(1–5).* Incidence rates for esophageal and gastric cardia adenocarcinomas are highest among white males, while rates for esophageal squamous cell carcinoma and noncardia gastric adenocarcinomas are highest among black males *(1,3).* The reasons underlying these contrasting patterns of incidence are unclear.

Tobacco smoking and alcohol use are strong risk factors for esophageal squamous cell carcinoma *(6),* whereas smoking is only weakly related to adenocarcinomas in the lower stomach *(7).* Several studies *(8–18)* have reported only a slight excess in risk of esophageal or gastric cardia adenocarcinomas associated with smoking and drinking. It has been suggested that patients with adenocarcinomas of the esophagus and gastric cardia have a higher income and more years of education than those with esophageal squamous cell carcinoma or noncardia gastric adenocarcinomas *(2,13,15).*

Esophageal adenocarcinomas are often located in the lower third of the esophagus near the gastroesophageal junction, and distinguishing adenocarcinomas arising in the lower esophagus from those arising in the gastro–esophageal junction are often very difficult *(19,20).* Tumors arising in the gastro–esophageal junction itself are classified by the Surveillance, Epidemiology, and End Results (SEER)[1] Program as being located in the gastric cardia *(21).*

Because of similar incidence patterns and anatomic proximity, it has been hypothesized that the origins of esophageal and gastric cardia adenocarcinomas are similar to one another and are distinct from the causes of esophageal squamous cell carcinoma and other gastric adenocarcinomas *(3).* To clarify this issue, we undertook a large collaborative, population-based study to identify risk factors for adenocarcinomas of the esophagus and gastric cardia. For comparison, we also determined risk factors for squamous cell carcinoma of the esophagus and noncardia adenocarcinomas of the stomach.

**Affiliations of authors:* M. D. Gammon, H. Ahsan, Division of Epidemiology, Columbia School of Public Health, New York, NY; J. B. Schoenberg, Applied Cancer Epidemiology Program, New Jersey Department of Health and Senior Services, Trenton; H. A. Risch, R. Dubrow, S. T. Mayne (Department of Epidemiology and Public Health), A. B. West (Department of Pathology), Yale University School of Medicine, New Haven, CT; T. L. Vaughan, J. L. Stanford, D. C. Farrow, Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA, and Department of Epidemiology, University of Washington School of Public Health, Seattle; W.-H. Chow, J. F. Fraumeni, Jr., Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; H. Rotterdam, Department of Pathology, College of Physicians & Surgeons of Columbia University, New York, NY; S. Niwa, Westat, Inc., Rockville, MD; W. J. Blot, International Epidemiology Institute, Rockville.

Correspondence to: Marilie D. Gammon, Ph.D., 622 W. 168th St., PH18-107, New York, NY 10032.

See ''Notes'' following ''References.''

Subjects and Methods

This multicenter, case–control study was conducted in three geographic areas of the United States with population-based tumor registries—the state of Connecticut, a 15-county area of New Jersey, and a three-county area of western Washington state. The goal of the collaborative effort was to identify, recruit, and interview four population-based case groups of roughly equal size containing subjects newly diagnosed with 1) esophageal adenocarcinoma, 2) gastric cardia adenocarcinoma, 3) esophageal squamous cell carcinoma, or 4) other gastric adenocarcinomas. The investigation was performed after approval from our institutional review boards and in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Potentially eligible case subjects were English-speaking men and women who were 30–79 years of age and who were diagnosed with primary invasive cancer of the esophagus or stomach from February 1, 1993, through January 31, 1995, in Connecticut; from April 1, 1993, through November 30, 1994, in New Jersey; and from March 1, 1993, through February 28, 1995, in Washington. All case subjects diagnosed with adenocarcinomas of the esophagus or gastric cardia (target case subjects) were considered eligible for the study. Those diagnosed with squamous cell carcinoma of the esophagus or adenocarcinomas located elsewhere in the stomach (comparison case subjects) were sampled by frequency matching to the expected distribution of the target case subjects on the basis of geographic area and 5-year age group in Connecticut, New Jersey, and Washington; on the basis of sex in New Jersey and Washington; and on the basis of race (white or other) in New Jersey.

All case subjects were identified by use of established rapid-reporting systems. Pathology reports were obtained for all potentially eligible case patients, and initial subject selection was based on the review of these records. Patients with tumors classified as not otherwise specified (NOS), mixed, or undifferentiated or with tumors of uncertain histologic type were initially considered eligible and approached for study participation, as were those with tumors in an unspecified subsite of the stomach. Final determination of case subject eligibility was based on a systematic review by the study pathologists (H. Rotterdam for New Jersey and A. B. West for Connecticut and Washington) using standardized criteria. The site of tumor origin was determined by a review of pathology slides and medical records, including pathology, radiology, surgery, and endoscopy reports. For tumors that involved the distal esophagus as well as the gastric cardia or proximal stomach, the site of origin was determined by estimating the location of the tumor's center using endoscopic, surgical, and pathologic data. Histologic slides of diagnostic biopsy and resection specimens and slides of tumor brushings and other cytologic preparations were reviewed in more than 99% of the cases. For those patients diagnosed with an indeterminate site of tumor origin by the initial study pathologist, records were rereviewed by the other study pathologist; disagreements were resolved by consensus.

Population-based control subjects were frequency matched to the expected distribution of target case subjects by 5-year age group and sex. Control subjects who were 30–64 years of age were identified by use of Waksberg's random-digit-dialing (RDD) method *(22);* those who were 65–79 years of age were identified by means of random sampling of Health Care Financing Administration (HCFA) rosters.

Face-to-face interviews were obtained for 554 (80.6%) of the eligible target case subjects, 589 (74.1%) of the eligible comparison case subjects, and 695 (73.7%) of the eligible control subjects. If the telephone screener response rate of 90.8% is taken into account for the 51.9% of control subjects who were identified by use of RDD, the overall response rate among control subjects was 70.2%. The primary reason for nonparticipation was subject refusal (12% of target case subjects, 17% of comparison case subjects, and 23.3% of control subjects), followed by physician refusal for case subjects (4% for each group). Interviews were administered directly to the study subject, rather than to the closest next of kin (usually the spouse), for 70.4% of the target case subjects, 67.8% of the comparison case subjects, and 96.6% of the control subjects. For case subjects, the mean length of time between cancer diagnosis and the interview was 3.7 months when the interview was conducted with the subject and 8.5 months when the interview was conducted with a proxy.

Prior to the interview, written informed consent was obtained from all subjects. During the interview, a structured questionnaire was administered by trained interviewers, and the average time to complete the questionnaire was 130 minutes. Information was collected on demographic characteristics, tobacco and alcohol use, other beverage consumption, medical history, use of medications, diet, and occupational history. The interview also elicited details on usual tobacco use anytime prior to 1 year before the interview, including the product type used (cigarettes, cigars, pipes, chewing tobacco, or snuff) as well as the intensity of its use, the age started and stopped, the total duration of use excluding the years stopped, and the years since last use for each type of product; for cigarette smoking, it was determined whether or not filtered cigarettes were used. A never smoker was defined as having smoked less than 100 cigarettes ever or having smoked less than one cigarette per day for 6 months or longer. An ex-smoker was defined as having stopped smoking 2 or more years before the interview. Alcohol consumption patterns were assessed by inquiring about the usual intake anytime prior to 1 year before the interview for each type of beverage separately, i.e., beer, wine, or liquor. A never drinker was defined as having consumed less than one drink per month. One drink was defined as 12 ounces of beer, 4 ounces of wine, or 1 ounce of hard liquor. The three types of alcohol were also combined to form an overall estimate of use.

Unconditional logistic regression was used to calculate odds ratios (ORs), as an estimate of the relative risk, and corresponding 95% confidence intervals (CIs) *(23)* for each of the four tumor types (esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and other gastric adenocarcinomas) and for the combined category of esophageal and gastric cardia adenocarcinomas in relation to tobacco, alcohol, education, and income. All models included as covariates the frequency-matched factors of geographic center (Connecticut/Washington/New Jersey, entered as indicator variables), age (in quartiles and entered as indicator variables), sex (female/male), and race (white/black/other, entered as indicator variables).

Logistic regression models were also used to adjust for the confounding effects of body mass index (BMI; expressed as weight in kilograms divided by the square of height in meters) (entered as a continuous variable) and income (entered as an ordered categoric variable). The 5% of persons with missing information on income were assigned values derived from simple regression models for case and control subjects that included age, race, sex, and education. Omission of subjects with missing income information from the logistic models did not materially alter the estimates of effect for tobacco, alcohol, education, or income. Inclusion of the imputed variables for these persons, however, permitted more precise estimates to be calculated for small subgroups of interest. Therefore, results from models that included all subjects are presented. In models that adjusted for the confounding effects of cigarette smoking, the factor was entered as an indicator variable (current smoker/ex-smoker/nonsmoker). Similarly, to adjust for the confounding effects of beer, hard liquor, and wine, each factor was entered as a dichotomous variable (ever/never). Subject characteristics that did not confound our results include education, family history of cancer, history of other medical conditions such as ulcers, use of various medications, and caloric intake.

Tests for trend in the ORs across exposure strata were calculated using logistic models that included continuous variables and, where appropriate, omitted never users. Potential effect modification between smoking and alcohol use or with other variables, such as age, sex, center, and race, was evaluated assuming a multiplicative model using logistic regression with cross-product terms representing the interaction between the two variables.

ORs and corresponding CIs derived from polytomous logistic regression models *(23)* for the four tumor types were nearly identical to those obtained from standard unconditional logistic regression. Thus, only the values obtained from the latter method are shown.

To compare two continuous variables, Pearson's correlation coefficient was calculated *(24).* Population attributable risk estimates were calculated *(25).* All reported *P* values are from two-sided tests.

Results

Table 1 shows the distribution of study participants according to demographic characteristics. Approximately 98% of the case subjects with esophageal and gastric cardia adenocarcinomas were white and 85% were males, whereas the corresponding percentages were 93% and 80% for the control subjects and 81% and 73% for the comparison case subjects. The median age at diagnosis was 66 years, with the case subjects being slightly older on average than the control subjects. About half of the study participants were from New Jersey (46.5%), while 30.9% were from Connecticut and 22.6% were from Washington.

Table 2 shows the estimates of risk according to tumor type

Table 1. Distribution of demographic characteristics among case subjects (by tumor type) and control subjects in Connecticut, New Jersey, and western Washington state, 1993–1995

Characteristic	Control subjects		Esophageal adenocarcinoma case subjects		Gastric cardia adenocarcinoma case subjects		Esophageal squamous cell carcinoma case subjects		Other gastric adenocarcinoma case subjects	
	No. (n = 695)	%	No. (n = 293)	%	No. (n = 261)	%	No. (n = 221)	%	No. (n = 368)	%
Age, y										
<57	179	25.8	76	25.9	65	24.9	34	15.4	65	17.7
57–64	178	25.6	48	16.4	56	21.5	53	24.0	61	16.6
65–71	176	25.3	79	27.0	71	27.2	74	33.5	93	25.3
>71	162	23.3	90	30.7	69	26.4	60	27.2	149	40.5
Sex										
Men	555	79.9	245	83.6	223	85.4	176	79.6	254	69.0
Women	140	20.1	48	16.4	38	14.6	45	20.4	114	31.0
Geographic center										
Connecticut	206	29.6	80	27.3	82	31.4	83	37.6	117	31.8
New Jersey	333	47.9	138	47.1	113	43.3	99	44.8	172	46.7
Washington	156	22.5	75	25.6	66	25.3	39	17.7	79	21.5
Race										
White	646	93.0	289	98.6	252	96.6	168	76.0	307	83.4
Black	34	4.9	2	0.7	4	1.5	48	21.7	36	9.8
Others	15	2.2	2	0.7	5	1.9	5	2.3	25	6.8

in relation to indicators of socioeconomic status. A decrease in risk for all types was noted with increasing levels of education or income; the inverse association with income was most pronounced for esophageal squamous cell carcinoma. The adjusted (for age, sex, geographic center, race, smoking, alcohol use, BMI, and education) ORs for esophageal adenocarcinoma and for gastric cardia adenocarcinoma were 0.5 (95% CI = 0.3–1.0) and 0.8 (95% CI = 0.4–1.6), respectively, among respondents with incomes of $75 000 per year or more compared with those with incomes of less than $15 000. Similarly, the corresponding adjusted ORs for graduate education compared with having less than a high school diploma were 0.7 (95% CI = 0.3–1.3) and 0.8 (95% CI = 0.4–1.6), respectively. Pearson's correlation coefficient between income and education among control subjects was .54 (P = .01).

Table 3 shows the estimates of risk associated with various patterns of cigarette smoking. With adjustments made for the confounding effects of age, sex, geographic center, race, BMI, income, and alcohol use, the risk of esophageal and gastric cardia adenocarcinomas was doubled among current smokers (OR = 2.2; 95% CI = 1.4–3.3 and OR = 2.6; 95% CI = 1.7–4.0, respectively) as well as among ex-smokers (OR = 2.0; 95% CI = 1.4–2.9 and OR = 1.9; 95% CI = 1.3–2.9, respectively). An increase in risk persisted up to 30 years after cigarette use had ceased. The adjusted ORs also increased with increasing years of smoking and with the number of cigarettes smoked per day for

Table 2. Adjusted* odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for esophageal adenocacinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and other gastric adenocarcinomas in relation to education and income

Characteristic	No. of control subjects	Esophageal adenocarcinoma case subjects		Gastric cardia adenocarcinoma case subjects		Esophageal squamous cell carcinoma case subjects		Other gastric adenocarcinoma case subjects	
		No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)
Education									
<12 years†	130	65	1.0	56	1.0	88	1.0	117	1.0
12 years	178	93	1.3 (0.9–2.1)	85	1.3 (0.8–2.0)	67	1.0 (0.6–1.6)	108	0.8 (0.5–1.1)
Vocational school	52	25	1.2 (0.7–2.2)	20	1.1 (0.6–2.1)	15	0.7 (0.3–1.5)	25	0.5 (0.3–0.9)
Some college	123	53	1.2 (0.7–2.0)	41	1.0 (0.6–1.7)	23	0.6 (0.3–1.1)	56	0.7 (0.4–1.0)
College graduate	118	39	1.0 (0.6–1.8)	36	0.9 (0.5–1.6)	19	0.8 (0.4–1.6)	36	0.6 (0.3–1.0)
Graduate school	94	18	0.7 (0.3–1.3)	23	0.8 (0.4–1.6)	9	0.7 (0.3–1.9)	25	0.6 (0.3–1.1)
Income, $ per y									
<15 000†	93	60	1.0	41	1.0	71	1.0	87	1.0
15 000–29 999	177	87	0.7 (0.4–1.1)	81	1.0 (0.6–1.6)	75	0.7 (0.4–1.1)‡	15	0.8 (0.6–1.3)
30 000–49 999	175	69	0.5 (0.3–0.8)	65	0.8 (0.5–1.3)	56	0.6 (0.3–1.1)	100	1.1 (0.7–1.7)
50 000–74 000	126	42	0.5 (0.3–1.0)	37	0.7 (0.4–1.4)	9	0.2 (0.1–0.4)	46	0.9 (0.5–1.5)
>75 000	124	35	0.5 (0.3–1.0)	37	0.8 (0.4–1.6)	10	0.2 (0.1–0.6)	20	0.5 (0.2–0.9)

*Adjusted for age; sex; geographic center (Connecticut, New Jersey, and Washington); race; body mass index (weight in kilograms divided by the square of height in meters); cigarette smoking; and use of beer, wine, and liquor.

†Reference category.

‡Two-sided test for trend; P for trend = .001.

Table 3. Adjusted* odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for esophageal adenocacinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and other gastric adenocarcinomas in relation to cigarette smoking

		Esophageal adenocarcinoma case subjects		Gastric cardia adenocarcinoma case subjects		Esophageal squamous cell carcinoma case subjects		Other gastric adenocarcinoma case subjects	
Cigarette smoking	No. of control subjects	No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)
Smoking status									
Never smoker†	244	63	1.0	53	1.0	22	1.0	106	1.0
Current smoker	155	86	2.2 (1.4–3.3)	85	2.6 (1.7–4.0)	108	5.1 (2.8–9.2)	96	1.8 (1.2–2.7)
Ex-smoker	296	144	2.0 (1.4–2.9)	123	1.9 (1.3–2.9)	91	2.8 (1.5–4.9)	164	1.5 (1.1–2.1)
Smoking cessation, y									
Stopped <11	74	44	2.7 (1.6–4.4)‡	45	2.9 (1.8–4.8)‡	47	5.6 (2.9–10.8)‡	50	1.8 (1.2–2.9)‡
Stopped 11–20	77	43	2.3 (1.4–3.8)	26	1.6 (0.9–2.8)	24	2.3 (1.1–4.8)	49	1.7 (1.0–2.7)
Stopped 21–30	78	31	1.9 (1.1–3.2)	34	2.2 (1.3–3.7)	8	1.0 (0.4–2.7)	34	1.5 (0.9–2.4)
Stopped >30	67	26	1.2 (0.7–2.2)	18	1.1 (0.6–2.0)	12	1.8 (0.8–4.2)	31	1.0 (0.6–1.8)
Smoking intensity (No./day)									
<16	134	49	1.5 (1.0–2.4)‡	42	1.4 (0.9–2.2)‡	44	2.7 (1.4–5.1)‡	82	1.5 (1.0–2.2)
16–20	148	78	2.2 (1.4–3.4)	71	2.2 (1.4–3.4)	62	3.9 (2.1–7.2)	94	1.7 (1.2–2.6)
21–30	71	49	3.1 (1.9–5.1)	46	3.1 (1.9–5.2)	36	5.3 (2.6–10.7)	30	1.4 (0.9–2.5)
>30	98	54	2.1 (1.3–3.3)	46	2.0 (1.2–3.3)	57	3.9 (2.0–7.6)	52	1.5 (1.0–2.4)
Duration of smoking, y									
<20	119	43	1.4 (0.9–2.2)‡	40	1.6 (1.0–2.6)‡	17	1.8 (0.9–3.7)‡	44	1.0 (0.7–1.6)‡
20–31	112	45	1.7 (1.0–2.8)	41	1.8 (1.1–2.9)	27	2.0 (1.0–4.0)	55	1.6 (1.0–2.4)
32–42	115	75	2.9 (1.8–4.4)	61	2.7 (1.7–4.2)	53	3.3 (1.8–6.1)	69	1.8 (1.2–2.7)
>42	105	66	2.4 (1.5–3.7)	66	2.9 (1.8–4.7)	99	5.9 (3.2–10.7)	90	2.1 (1.4–3.1)
Pack-years§									
<14	115	38	1.4 (0.8–2.2)‡	24	0.9 (0.5–1.6)‡	23	2.0 (1.0–4.0)‡	51	1.2 (0.8–1.8)‡
14–31	111	40	1.6 (1.0–2.6)	52	2.3 (1.4–3.6)	30	2.8 (1.4–5.5)	59	1.5 (1.0–2.4)
32–54	121	76	2.9 (1.8–4.5)	69	2.8 (1.8–4.4)	62	4.5 (2.4–8.5)	74	1.7 (1.2–2.6)
>54	104	76	2.8 (1.8–4.4)	60	2.5 (1.5–4.1)	84	5.8 (3.1–11.0)	74	2.1 (1.3–3.2)
Filter status									
Filtered only	240	120	2.0 (1.4–2.9)	109	2.1 (1.4–3.1)	95	2.9 (1.7–5.0)	139	1.6 (1.1–2.2)
Filtered and nonfiltered	62	29	1.7 (1.0–3.0)	23	1.5 (0.8–2.7)	26	2.7 (1.4–5.6)	28	1.1 (0.6–1.9)
Nonfiltered only	148	76	1.9 (1.2–2.9)	73	2.1 (1.3–3.2)	74	3.6 (2.0–6.4)	88	1.5 (1.0–2.3)

*Adjusted for age; sex; geographic center (Connecticut, New Jersey, and Washington); race; body mass index (weight in kilograms divided by the square of height in meters); income; and use of beer, wine, and liquor.

†The reference category for all estimates in this table is ''Never smoker'' (*see* ''Subjects and Methods'' section for explanation of smoker classification).

‡Two-sided tests for trend; all P for trend $\leq .05$.

§Pack-years = the number of packs per day multiplied by the number of years smoking.

both tumors, but risks were similar in users of filtered and nonfiltered cigarettes.

For subjects with esophageal squamous cell carcinoma, the adjusted OR associated with current cigarette smoking was 5.1 (95% CI = 2.8–9.2) but the OR dropped to 2.3 (95% CI = 1.1–4.8) by 11–20 years after smoking cessation and to 1.8 (95% CI = 0.8–4.2) 30 years after quitting smoking. For noncardia gastric adenocarcinomas, the ORs were 1.8 (95% CI = 1.2–2.7) and 1.5 (95% CI = 1.1–2.1) for current and ex-smokers, respectively.

Case subjects with esophageal and gastric cardia adenocarcinomas were not more likely than control subjects or comparison case subjects to use other tobacco products, including cigars, pipes, chewing tobacco, or snuff (data not shown).

Table 4 shows the ORs for alcohol intake. With adjustments made for smoking and other confounders, adenocarcinomas of the esophagus, the gastric cardia, or other gastric sites did not appear to be associated with drinking beer or hard liquor. In contrast, the risk of esophageal squamous cell carcinoma was doubled in relation to ever use of beer and tripled in relation to ever use of liquor. The risk estimates rose with increasing consumption of either product for this type of tumor. Ever drinking of wine was associated with a decreased risk of adenocarcinomas of the esophagus (OR = 0.6; 95% CI = 0.4–0.8) and gastric cardia (OR = 0.6; 95% CI = 0.5–0.9) as well as a reduced risk of esophageal squamous cell carcinoma (OR = 0.6; 95% CI = 0.4–0.9) and of noncardia gastric adenocarcinomas (OR = 0.7; 95% CI = 0.5–0.9). However, there was no apparent trend in risk with increasing number of drinks of wine per week.

Also shown in Table 4 are the risks associated with a combined estimate of alcohol consumption in comparison with never use of any type of alcohol. Risk in relation to total alcohol intake was decreased 30% (OR = 0.7; 95% CI = 0.5–1.0) for esophageal adenocarcinoma, 30% (OR = 0.7; 95% CI = 0.5–1.1) for gastric cardia adenocarcinoma, and 20% (OR = 0.8; 95% CI = 0.6–1.1) for nongastric cardia adenocarcinomas; however, none of the reductions in risk was statistically significant. In contrast, the risk of esophageal squamous cell carcinoma was significantly elevated 3.5-fold (OR = 3.5; 95% CI = 1.9–6.2) for ever versus never users of any alcoholic beverage; this risk increased with rising levels of intake reaching an OR of 7.4 (95% CI = 4.0–13.7) among those who consumed more than 30 alcoholic drinks per week.

Since the patterns of risk observed in this study were similar for adenocarcinomas of the esophagus and gastric cardia, the cases were combined for additional analyses (Table 5). Risk associations with the highest levels of income and education, compared with the lowest, were decreased (OR = 0.6; 95% CI = 0.4–1.1 and 0.7; 95% = 0.4–1.3, respectively), but the re-

Table 4. Adjusted* odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and other gastric adenocarcinomas in relation to alcohol consumption by type

Type of alcohol	No. of control subjects	Esophageal adenocarcinoma case subjects		Gastric cardia adenocarcinoma case subjects		Esophageal squamous cell carcinoma case subjects		Other gastric adenocarcinoma case subjects	
		No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)
Beer									
Never†	310	130	1.0	116	1.0	57	1.0	200	1.0
Ever	385	163	0.9 (0.6–1.2)	145	0.8 (0.6–1.2)	164	2.2 (1.4–3.3)	166	0.8 (0.6–1.1)
Drinks/wk									
<2	86	35	0.9 (0.6–1.5)	22	0.6 (0.4–1.1)	22	1.4 (0.7–2.7)‡	42	0.8 (0.5–1.3)
2–4	112	35	0.7 (0.4–1.1)	40	0.9 (0.5–1.4)	18	1.1 (0.5–2.1)	35	0.6 (0.4–1.0)
5–12	98	30	0.6 (0.3–0.9)	38	0.8 (0.5–1.2)	32	1.7 (0.9–3.0)	35	0.7 (0.4–1.1)
>12	89	58	1.1 (0.7–1.7)	43	0.9 (0.6–1.5)	83	2.6 (1.6–4.4)	47	0.9 (0.5–1.4)
Liquor									
Never†	320	130	1.0	116	1.0	48	1.0	188	1.0
Ever	375	161	1.2 (0.9–1.7)	145	1.0 (0.7–1.4)	173	3.1 (2.0–4.8)	177	1.0 (0.8–1.4)
Drinks/wk									
<2	106	35	0.9 (0.5–1.4)	35	1.0 (0.6–1.5)	19	1.4 (0.8–2.8)‡	58	1.2 (0.8–1.9)
2–4	85	33	1.1 (0.7–1.9)	32	1.1 (0.7–1.9)	18	1.6 (0.8–3.2)	37	1.0 (0.6–1.6)
5–14	116	52	1.2 (0.8–1.9)	51	1.0 (0.6–1.7)	46	2.2 (1.3–3.7)	45	0.8 (0.5–1.2)
>14	64	34	1.2 (0.7–2.0)	24	0.8 (0.4–1.4)	82	5.4 (3.1–9.2)	33	0.9 (0.5–1.6)
Wine									
Never†	389	205	1.0	176	1.0	149	1.0	258	1.0
Ever	306	88	0.6 (0.4–0.8)	84	0.6 (0.5–0.9)	72	0.6 (0.4–0.9)	108	0.7 (0.5–0.9)
Drinks/wk									
<2	106	34	0.7 (0.5–1.2)	30	0.7 (0.4–1.1)	17	0.6 (0.3–1.1)	44	0.8 (0.5–1.2)
2–3	48	12	0.6 (0.3–1.2)	12	0.6 (0.3–1.2)	8	0.6 (0.3–1.5)	9	0.4 (0.2–0.9)
4–7	98	27	0.6 (0.4–0.9)	20	0.5 (0.3–0.8)	18	0.7 (0.4–1.3)	38	0.8 (0.5–1.2)
>7	50	13	0.5 (0.2–0.9)	19	0.8 (0.5–1.5)	25	0.8 (0.4–1.4)	16	0.6 (0.3–1.1)
Any alcohol									
Never†	172	79	1.0	63	1.0	19	1.0	125	1.0
Ever	523	210	0.7 (0.5–1.0)	196	0.7 (0.5–1.1)	195	3.5 (1.9–6.2)	238	0.8 (0.6–1.1)
Drinks/wk									
<5	161	56	0.7 (0.4–1.0)	46	0.6 (0.4–1.0)	16	0.8 (0.4–1.6)‡	74	0.7 (0.5–1.1)
5–11	134	45	0.6 (0.4–0.9)	59	0.8 (0.5–1.3)	25	1.8 (0.9–3.5)	68	0.9 (0.6–1.3)
12–30	138	57	0.7 (0.4–1.1)	52	0.7 (0.4–1.1)	48	2.9 (1.5–5.4)	55	0.7 (0.4–1.0)
>30	90	52	0.9 (0.5–1.4)	39	0.7 (0.4–1.2)	106	7.4 (4.0–13.7)	41	0.6 (0.4–1.0)

*Adjusted for age; sex; geographic center (Connecticut, New Jersey, and Washington); race, body mass index (weight in kilograms divided by the square of height in meters); income; cigarette smoking; and all other types of alcohol use.

†Reference category (*see* ''Subjects and Methods'' section for explanation of drinker classification).

‡Two-sided tests for trend; all P for trend $\leq .05$.

ductions were not statistically significant. A greater than twofold increase in risk was associated with ever smoking of cigarettes, which persisted up to 30 years after quitting. Attributable risk calculations revealed that 41% of all esophageal and gastric cardia adenocarcinomas combined are attributable to cigarette smoking (data not shown).

As also shown in Table 5, there was no association between adenocarcinomas of the esophagus and gastric cardia and the consumption of beer or liquor, but a reduction in risk was seen with ever drinking of wine (OR = 0.6; 95% CI = 0.5–0.8). There was little heterogeneity in the ORs for esophageal and gastric cardia adenocarcinomas combined, or for the other tumor types, in relation to smoking, drinking, or socioeconomic status across subgroups categorized by age, sex, geographic center, or race (data not shown).

Table 6 shows the estimates of risk for the four tumor types in relation to cigarette smoking stratified by alcohol drinking. The adjusted ORs for subjects who both smoked and drank were not substantially different from those who just smoked. Although the risk of esophageal squamous cell carcinoma more than doubled among smokers and wine drinkers (OR = 6.8; 95% CI = 2.2–21.1) compared with just smokers (OR = 2.8; 95% CI = 1.5–5.3), the apparent effect modification was not statistically significant (P = .39).

The statistical analyses were repeated using a sample restricted to only subjects who were interviewed directly, i.e., excluding subjects with proxy respondents (data not shown). In this restricted sample, the risk estimates for the four tumor types in relation to smoking and drinking varied little from those obtained in analyses that included all participants. Thus, only the analyses based on the entire sample are presented.

Discussion

In this examination of tobacco, alcohol, and socioeconomic factors, we found similar estimates of effect for the development of esophageal and gastric cardia adenocarcinomas. When the two tumor types were combined, risk was reduced 40% in relation to an income of $75 000 or more and reduced 30% in relation to a graduate school education. Risk was increased 2.4 times in relation to currently smoking cigarettes, but it was unaffected by alcohol drinking, except for a 40% decrease associated with wine drinking. Risk estimates associated with income, education, and smoking status were similar in direction

Table 5. Adjusted* odds ratios (ORs) and 95% confidence intervals (CIs) for esophageal and gastric cardia adenocarcinomas combined in relation to education, income, cigarette smoking, and alcohol consumption

Characteristic	No. of control subjects	Esophageal and gastric cardia adenocarcinoma case subjects	
		No.	OR (95% CI)
Education			
<12 years†	130	121	1.0
12 years	178	178	1.3 (0.9–1.9)
Vocational school	52	45	1.2 (0.7–1.9)
Some college	123	94	1.1 (0.7–1.7)
College graduate	118	75	1.0 (0.6–1.5)
Graduate school	94	41	0.7 (0.4–1.3)
Income, $ per y			
<15 000†	93	101	1.0
15 000–29 999	177	168	0.8 (0.5–1.2)
30 000–49 999	175	134	0.6 (0.4–0.9)
50 000–74 000	126	79	0.6 (0.4–1.0)
>75 000	124	72	0.6 (0.4–1.1)
Cigarette smoking			
Never smoker†	244	116	1.0
Current smoker	155	171	2.4 (1.7–3.4)
Ex-smoker	296	267	2.0 (1.5–2.7)
Smoking cessation, y			
Stopped <11	74	89	2.9 (1.9–4.3)‡
Stopped 11–20	77	69	1.9 (1.3–3.0)
Stopped 21–30	78	65	1.9 (1.3–3.0)
Stopped >30	67	44	1.2 (0.8–2.0)
Beer			
Never†	310	246	1.0
Ever	385	308	0.8 (0.6–1.1)
Drinks/wk			
<2	86	57	0.8 (0.5–1.2)
2–4	112	75	0.8 (0.6–1.2)
5–12	98	68	0.7 (0.4–1.0)
>12	89	101	1.0 (0.7–1.5)
Liquor			
Never†	320	246	1.0
Ever	375	306	1.1 (0.8–1.4)
Drinks/wk			
<2	106	70	0.9 (0.6–1.4)
2–4	85	65	1.1 (0.7–1.7)
5–14	116	103	1.1 (0.8–1.5)
>14	64	58	1.0 (0.6–1.5)
Wine			
Never†	389	381	1.0
Ever	306	172	0.6 (0.5–0.8)
Drinks/wk			
<2	106	64	0.7 (0.5–1.0)
2–3	48	24	0.6 (0.3–1.0)
4–7	98	47	0.5 (0.3–0.8)
>7	50	32	0.7 (0.4–1.1)
Any alcohol			
Never†	172	142	1.0
Ever	523	412	0.8 (0.6–1.0)
Drinks/wk			
<5	161	102	0.7 (0.5–0.9)
5–11	134	104	0.7 (0.5–1.0)
12–30	138	109	0.7 (0.5–1.0)
>30	90	91	0.8 (0.5–1.2)

*ORs are adjusted for age; sex; geographic center (Connecticut, New Jersey, and Washington); body mass index (weight in kilograms divided by the square of height in meters); and all other variables in the table.

†Reference category (*see* ''Subjects and Methods'' section for explanation of smoker and drinker classifications).

‡Two-sided test for trend; P for trend = .005.

to those observed for the development of noncardia gastric adenocarcinomas and esophageal squamous cell carcinoma, although the risks were higher for the development of esophageal squamous cell carcinoma. The risk associated with wine consumption was reduced for all tumor types in our study, but the risks for beer and liquor intake were elevated twofold and threefold, respectively, for the development of esophageal squamous cell carcinoma.

To our knowledge, this investigation is the largest population-based study of esophageal and gastric adenocarcinomas conducted to date. The study encompassed all incident cases of cancer of the esophagus and stomach identified in three geographic areas of the United States, with a standardized review of pathology specimens and medical records to assign the site of tumor origin and to confirm the histologic type. A comprehensive, personal questionnaire, which was administered by trained interviewers, was employed in the data collection. Despite this systematic approach, some limitations of the study must be considered when interpreting our results.

One problem relates to the difficulty of determining the exact site of origin for tumors arising near the gastro–esophageal junction. Thus, it is possible that misclassification of adenocarcinomas of the lower esophagus and the gastric cardia may contribute to the similar patterns of risk noted for these tumors.

Although the incidence rates for esophageal and gastric adenocarcinomas have risen dramatically over time, these tumors are still relatively uncommon, which limits our ability to identify subgroup effects. To maximize study efficiency, the comparison case subjects (i.e., those with esophageal squamous cell carcinoma or noncardia gastric adenocarcinomas) were frequency matched to the expected distribution of the target case subjects (i.e., those with esophageal and gastric cardia adenocarcinomas) on the basis of age and geographic area at all three centers; on the basis of sex in New Jersey and Washington; and on the basis of race in New Jersey. Because comparison cases were matched to target cases on the basis of race (and incidence rates for these latter tumors are higher among whites than among blacks), the comparison case subjects in our study do not reflect the underlying distributions for all cases of esophageal squamous cell carcinoma or noncardia gastric adenocarcinomas, for which incidence rates are substantially higher among blacks than among whites.

Approximately 30% of our case subject interviews were conducted with a proxy respondent whose knowledge of the exposure status of the case subject may be incomplete *(26)*. However, it is reassuring that analyses restricted to subjects with self-reports yielded results similar to analyses for all study participants, including those with next-of-kin interviews. Others *(27)* have also found that use of proxy-reported responses for cigarette smoking do not yield substantially biased estimates.

Our findings from this large case–control study are consistent with earlier population-based studies *(13,15)* implicating cigarette smoking as a risk factor for esophageal and gastric cardia adenocarcinomas. The 140% increase in risk among current smokers observed in our data was not as great as that observed for squamous cell carcinoma of the esophagus, but it was slightly higher than the excess risk observed for adenocarcinomas of the lower stomach. It is noteworthy that the risk for esophageal and gastric cardia adenocarcinomas among ex-smokers persisted at this elevated level for more than 20 years. On the basis of attributable risk calculations, 41% of all esophageal and gastric cardia adenocarcinomas in the three study areas is attributable to cigarette smoking.

Table 6. Adjusted* odds ratios (ORs) and 95% confidence intervals (CIs) for esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, other gastric adenocarcinomas in relation to cigarette smoking and according to beer, liquor, and wine consumption

		Esophageal adenocarcinoma case subjects		Gastric cardia adenocarcinoma case subjects		Esophageal squamous cell carcinoma case subjects		Other gastric adenocarcinoma case subjects	
Drinking status	Smoking status	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Beer	Cigarettes								
No	No†	1.0		1.0		1.0		1.0	
	Yes	2.0	1.2–3.3	1.8	1.1–3.0	2.5	1.1–5.6	1.6	1.1–2.5
Yes	No†	1.0		1.0		1.0		1.0	
	Yes	2.1	1.2–3.6	2.7	1.5–4.9	5.2	2.4–11.5	1.4	0.9–2.3
Liquor	Cigarettes								
No	No†	1.0		1.0		1.0		1.0	
	Yes	2.4	1.5–3.9	2.0	1.2–3.2	2.6	1.1–6.2	1.4	0.9–2.1
Yes	No†	1.0		1.0		1.0		1.0	
	Yes	1.9	1.1–3.2	3.0	1.6–5.6	4.8	2.3–10.2	2.0	1.2–3.4
Wine	Cigarettes								
No	No†	1.0		1.0		1.0		1.0	
	Yes	2.4	1.6–3.7	2.0	1.3–3.1	2.8	1.5–5.3	1.3	0.9–1.9
Yes	No†	1.0		1.0		1.0		1.0	
	Yes	1.7	0.9–3.1	2.7	1.4–5.3	6.8	2.2–21.1	2.2	1.2–4.0

*Adjusted for age; sex; geographic center (Connecticut, New Jersey, and Washington); race; body mass index (weight in kilograms divided by the square of height in meters); income; and the other two types of alcohol.

†Reference category.

No decline in the risk of esophageal and gastric cardia adenocarcinomas was evident until 30 years after smoking cessation, which is in contrast to the steady decrease in risk observed after quitting for esophageal squamous cell carcinoma. These patterns suggest that smoking may affect an early stage in the induction of esophageal and gastric cardia adenocarcinomas, whereas later stages are involved for esophageal squamous cell carcinoma. As a result, the time trends in smoking prevalence may have contributed to the divergent incidence trends for these tumors. Thus, the declining incidence of esophageal squamous cell carcinoma since the 1970s is consistent with the reduced prevalence of cigarette smoking among American men that began in the 1960s. On the other hand, the rise in the prevalence of smoking among American men from the early part of this century until the 1960s, allowing for a lag of 30 years, coincides with the rising incidence of esophageal and gastric cardia adenocarcinomas, at least among older age groups. The recent national decline in smoking prevalence may not yet have had an impact on the trends for esophageal and gastric adenocarcinomas.

Although our study found no excess risk of esophageal and gastric cardia adenocarcinomas associated with the consumption of beer or hard liquor, there was an inverse association seen for wine drinking that extended to all four tumor types. If the reduction in risk is real, there may be a protective ingredient in wine, such as resveratrol *(28)*, that is not present in beer or liquor. However, previous population-based case–control studies in the United States *(13,15)* have generally found no association between wine drinking and the risk of esophageal and gastric cardia adenocarcinomas. In comparison with these studies, the prevalence of wine consumption in our population-based control subjects appears to have been elevated, and it was higher among those who were male, white, and younger in age and who also reported a higher income, education, and intake of beer and liquor (data not shown). Thus, it is possible that the reduced risks associated with wine intake in our study are the result of sampling bias or perhaps of residual confounding.

Among persons in our study who reported both smoking cigarettes and drinking any type of alcohol, risk was not substantially greater for developing adenocarcinomas of the esophagus, the gastric cardia, or other gastric sites than for individuals who only reported smoking. The smoking-associated risk of esophageal squamous cell carcinoma, however, was more than twice as high among drinkers of any type of alcohol than among nondrinkers, which is consistent with other studies of this tumor *(29)*.

Our finding of a reduced risk of esophageal and gastric cardia adenocarcinomas among those with higher income levels confirms the results of earlier studies that were population-based and conducted in the United States *(13,15)*. The findings for education, however, are inconsistent. Whereas Brown et al. *(13)* noted a reduction in risk with decreasing education, the results of Vaughan et al. *(15)* resemble our results in showing slightly increasing risks with decreasing education.

In summary, our large population-based, case–control study of esophageal and gastric cardia adenocarcinomas revealed a doubling of risk among current and ex-smokers, a risk that persisted for nearly 30 years after smoking cessation, and a nonsignificant decrease in risk associated with higher incomes. No association was noted for beer or hard liquor intake, but a 40% reduced risk was associated with wine drinking. These patterns were similar to those observed for noncardia gastric adenocarcinomas. In contrast, the risks of developing esophageal squamous cell carcinoma were estimated to be more than five times higher among current smokers, 2.8-times higher among ex-smokers, and more than three times higher among liquor drinkers. Our findings suggest that smoking affects an early stage in the development of esophageal and gastric adenocarcinomas and may have contributed to the recent increases reported in the incidence of these tumors, especially among older persons.

References

(1) Yang PC, Davis S. Incidence of cancer of the esophagus in the US by histologic type. Cancer 1988;61:612–7.

(2) Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer 1990;62:440–3.
(3) Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA1991;265: 1287–9.
(4) Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. Eur J Cancer Prev 1992;1:265–9.
(5) Blot WJ, Devesa SS, Fraumeni JF Jr. Continuing climb in rates of esophageal adenocarcinoma: an update [letter]. JAMA 1993;270:1320.
(6) Day NE, Munoz N. Esophagus. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York: Oxford Univ Press, 1996: 681–706.
(7) Nomura A. Stomach. In: Schottenfeld D, Fraumeni JF Jr., editors. Cancer epidemiology and prevention. New York: Oxford Univ Press, 1996: 707–24.
(8) Wu-Williams AH, Yu MC, Mack TM. Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles County. Cancer Res 1990; 50:2569–76.
(9) Gray JR, Coldman AJ, MacDonald WC. Cigarette and alcohol use in patients with adenocarcinoma of the gastric cardia or lower esophagus. Cancer 1992;69:2227–31.
(10) Newcombe PA, Carbone PP. The health consequences of smoking. Cancer Med Clin North Am 1992;76:305–31.
(11) Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. Cancer Causes Control 1993;4:123–32.
(12) Palli D, Bianchi S, Dacarli A, Cipriani F, Avellini C, Cocco P, et al. A case-control study of cancers of the gastric cardia in Italy. Br J Cancer 1992;65:263–6.
(13) Brown LM, Silverman DT, Pottern LM, Schoenberg JB, Greenberg RS, Swanson GM, et al. Adenocarcinomas of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. Cancer Causes Control 1994;5:333–40.
(14) Gonzalez CA, Agudo A, Montes J, Riboli E, Sanz JM. Tobacco and alcohol intake in relation to adenocarcinoma of the gastric cardia in Spain. Cancer Causes Control 1994;5:88–9.
(15) Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995;4:85–92.
(16) Zhang ZF, Kurtz RC, Sun M, Karpeh M Jr, Yu GP, Gargon N, et al. Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol, and socioeconomic factors. Cancer Epidemiol Biomarkers Prev 1996;5:761–8.
(17) Ji BT, Chow WH, Yang G, McLaughlin JK, Gao RN, Zheng W, et al. The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. Cancer 1996;77:2449–57.
(18) Garidou A, Tzonou A, Lipworth L, Signorello LB, Kalapothaki V, Trichopoulos D. Life-style factors and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. Int J Cancer 1996; 68:295–9.
(19) Kalish RJ, Clancy PE, Orringer MB, Appelman HD. Clinical, epidemiologic, and morphologic comparison between adenocarcinomas arising in Barrett's esophageal mucosa and in the gastric cardia. Gastroenterology 1984;86:461–7.
(20) Wang HH, Antonioli DA, Goldman H. Comparative features of esophageal and gastric adenocarcinomas: recent changes in type and frequency. Hum Pathol 1986;17:482–7.
(21) Surveillance, Epidemiology, and End Results (SEER) Program. Special Public Use Tape *(1973–90).* National Cancer Institute, DCPC, Surveillance Program, Cancer Statistics Branch, November 1993.
(22) Waksberg J. Sampling methods for random digit dialing. J Am Stat Assoc 1978;73:40–6.
(23) Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, 1989.
(24) Armitage P. Statistical methods in medical research. Oxford: Blackwell Scientific Publ, 1971.
(25) Rothman KJ. Modern epidemiology. Boston: Little, Brown, 1986.
(26) Nelson LM, Longstreth WT Jr, Koepsell TD, van Belle G. Proxy respondents in epidemiologic research. Epidemiol Rev 1990;12:71–86.
(27) McLaughlin JK, Dietz MS, Mehl ES, Blot WJ. Reliability of surrogate information on cigarette smoking by type of informant. Am J Epidemiol 1987;126:144–6.
(28) Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997;275:218–20.
(29) Longnecker MP, Enger SM. Epidemiologic data on alcoholic beverage consumption and risk of cancer. Clin Chim Acta 1996;246:121–41.

Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

Present address: A. B. West, Department of Pathology, The University of Texas, Galveston.

Present address: J. L. Stanford, Department of Oncological Sciences, Utah Cancer Registry, University of Utah, Salt Lake City.

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